DETAILED ACTION

Claim Status

1. Claim 7 has been cancelled. Claims 1-6 and 8-12 are under consideration in this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-6 and 8-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dalemans et al., (WO 99/30733 published June 24, 1999) in view of Volkin et al., (WO 00/02591 published January 20, 2000).

The rejection is maintained on the grounds that Dalemans et al., in view of Volkin et al., teach an immunogenic composition suitable for administration to a vertebrate host which comprises: a composition comprising a protein antigen immunogenic component comprising at least one protein antigen selected from the group consisting of model protein antigens and immunogenic protein antigens and a mineral-based, negatively charged adjuvant; and (b) a polynucleotide immunogenic component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said polynucleotide immunogenic component into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a

prophylactic or therapeutic immune, said composition produced by a method comprising preincubating or subsequently mixing said mineral-based negatively charged adjuvant with said at least one protein antigen immunogenic component to form the composition of (a) prior to formulating with said polynucleotide immunogenic component.

Response to Arguments

3. Applicant's arguments filed September 1, 2010 have been fully considered but they are not persuasive.

Applicants argue that the present invention results on the one hand in a vaccine with a different appearance (see p.6, 1.21-25 of the application as filed). Page 6, lines 21-25 disclose that the seemingly different appearance has been extensively described by WO 00/2591, which is the Volkin et al., reference. Therefore the rejection of record, which includes that same Volkin et al., reference, addresses the adjuvant, delivered in conjunction , e.g. incubated or pre-mixed with a suitable protein.

Applicants assert that "on the other hand (as a consequence) in a vaccine capable of differentiating the immune response with regard to the Th1 and Th2 response, but not in the sense that you get a mixed Th1/Th2 response to each of the vaccine components (DNA and protein), but instead a non-discriminatory Th-1 and Th-2 response. It is noted that Dalemans et al., in view of Volkin et al, teach every single limitation of the immunogenic compositions. Moreover, the instant specification recites that the antigens encoded by DNA vaccines would preferentially prime Th1 immunity while the antigens formulated into the $AlPO_4$ as recombinant proteins would

preferentially induce Th2 immunity. Applicants agree that Dalemans et al., teach antigens encoded by DNA vaccines would preferentially prime Th1 immunity with the antigens formulated into the AlPO4 as recombinant proteins that would preferentially induce Th2 immunity. Dalemans et al., teach inducing a Th2 response when using protein based vaccines which elicit a predominantly Th2 response; Dalemans et al., teach both Th1 and Th2 responses being elicited and the combination of polynucleotide/polypeptide appear to act synergistically (page 7, lines 10-17). Therefore Dalemans et al., teach stimulating a Th2 response, thereby teaching applicants unclaimed assertions drawn to differentiation.

Applicants argue that the vaccine formulations are structurally different from vaccine formulations because the adjuvant has not been pre-incubated; however it is noted that the features upon which applicant relies i.e., vaccine formulations in which the adjuvant has been pre-incubated are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims recite preincubating or subsequently mixing the adjuvant. While the specification at paragraph [0035] states that when the adjuvant is delivered in conjunction, e.g., pre-incubated or pre-mixed with the protein, there is a different appearance, it is the position of the office that Dalemans et al., teach the protein antigen being adsorbed to alum. Therefore, Dalemans et al., teach adjuvant being delivered in

conjunction, e.g., pre-incubated or pre-mixed with the protein; therefore the prior teach preincubating or subsequently mixing the adjuvant jus as required by the claims.

It is noted that Applicants do not argue that Dalemans et al., in view of Volkin et al., fail to any actual component of the instantly claimed immunogenic compositions. Applicants are reminded that Dalemans et al., in view of Volkin et al., teach each and every instantly recited component of the immunogenic composition.

Applicants assert that Dalemans et al, does not relate to differentiating and pre-determining the immunological response. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., differentiating and pre-determining the immunological response) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, applicants' assertion is not persuasive.

The claims recite inducing a prophylactic or therapeutic immune response or the immunogenic composition being capable of inducing a prophylactic or therapeutic Th1 and Th2 immune response. Applicants concede that Dalemans reports a balanced Th1/Th2 response. Dalemans et al., teach enhancing the immune response that can stimulate protective immunity where the composition increases both the humoral and cell mediated immune responses (page 3-4, lines 28- 4). Therefore Dalemans et al., in view of Volkin et al, teach both inducing a prophylactic or therapeutic immune response

and immunogenic compositions capable of inducing a prophylactic or therapeutic Th1 and Th2 immune response.

Applicants urge that the combination vaccine of a DNA component and a protein antigen always lead to a Th1 response, irrespective of adjuvants and that the addition of adjuvants is optional. Applicants are reminded that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Therefore applicant's argument is not persuasive especially when considering that Dalemans et al., disclose a section entitled Adjuvants covering pages 9-10. Dalemans et al., state that the polynucleotides, polypeptide and polynucleotide + polypeptide mixture (complex) are preferably adjuvanted in the vaccine formulation. Dalemans et al, then recite suitable adjuvants and suitable adjuvant systems. The Dalemans et al., reference is relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including preferred the inclusion of adjuvants. The fact the Dalemans et al., do not require adjuvants does mean that Dalemans et al., do not teach adjuvants. Therefore Dalemans et al., specifically and clearly disclose the adjuvants of the claim as recited by the instant claim.

Applicants assert that Volkin et al., teach a negatively charged mineral-based adjuvant leads to an enhanced Th1 immunological response, but does not differentiate the immunological response. However, the claims only require inducing a prophylactic or therapeutic immune response or the immunogenic composition being capable of

inducing a prophylactic or therapeutic Th1 and Th2 immune response and do not recite differentiation. Volkin et al., teach the adjuvanted composition will increase the immune response (page 5, lines 5-7). Volkin et al., aluminum phosphate being negatively charged and such adjuvants more than capable of stimulating IL-4 and T_H2-type of helper T cells as well as increasing levels of IgG1 and IgE antibodies (page 3, lines 17-24). The prior art teach inducing a prophylactic or therapeutic immune response or the immunogenic composition being capable of inducing a prophylactic or therapeutic Th1 and Th2 immune response.

Therefore, applicants repeated assertions about the lack differentiation and pre-determination is not persuasive. In response to applicant's argument that Dalemans et al., in view of Volkin et al., do not teach differentiation and pre-determination, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In this, the was disclosed nor the specific result end result. However, the prior art structure of Dalemans et al., in view of Volkin et al., have the same components, (a) a composition comprising a protein antigen immunogenic component comprising at least one protein antigen selected from the group consisting of model protein antigens and immunogenic protein antigens and a mineral-based, negatively charged adjuvant; and a polynucleotide immunogenic component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said polynucleotide immunogenic component into said vertebrate

host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune response; said composition produced by a method comprising preincubating or subsequently mixing said mineral-based negatively charged adjuvant with said at least one protein antigen immunogenic component to form the composition of (a) prior to formulating with said polynucleotide immunogenic component.

The claims are to an immunogenic composition suitable for administration to a vertebrate host and method of making the combined immunogenic composition; not to the problem of differentiating and pre-determining the immunological response.

Applicants argue that a person skilled in the art would have no motivation to combine Dalemans et al., in view of Volkin et al., since both relate at best to an enhanced but not differentiated and pre-determined immune response.

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, it would have been obvious to modify the immunogenic composition suitable for

administration to a vertebrate host which comprises a protein antigen and a an adjuvant and a polynucleotide immunogenic component as taught by Dalemans et al., wherein the modification simply includes a mineral-based, negatively charged adjuvant as taught by Volkin et al., in order to advantageously provide an increased immune response and decrease nuclease digestion of the polynucleotide immunogenic component within the vertebrate host subsequent to immunization.

Applicants argue that there is no teaching for replacing the positively charged mineral-based adjuvant of Dalemans with the adjuvant of Volkin et al. Dalemans et al., clearly and specifically recites that suitable adjuvants, including aluminum salt such as aluminum hydroxide gel (alum), aluminum phosphate or algammulin, but may also be a salt of calcium, iron or zinc; beginning at page 9, lines 23. Furthermore, Dalemans et al., teach the protein antigen being adsorbed to alum (page 11, lines 3-6). Finally, in Example 9, Dalemans et al., recite administration of both DNA and the protein antigen further including alum, as the one mineral-based negatively charged adjuvant. Therefore repeatedly Dalemans et al., teach the inclusion of a mineral-based negatively charged adjuvant, contrary to applicants' assertions.

Applicants are reminded that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Therefore applicant's argument is not persuasive especially when considering that Dalemans et al., disclose recite

administration of both DNA and the protein antigen further including alum, as the one mineral-based negatively charged adjuvant. Therefore Dalemans et al., specifically and clearly discloses all the elements of the claim within the four corners of the document as arranged by the instant claim. Applicants are clear that Dalemans et al., teach a mineral-based, negatively charged adjuvant. Volkin et al., teach DNA vaccine formulations wherein the adjuvant comprises mineral-based particles which are negatively charged and the particles possess a sufficient negative charge as to substantially retard binding to the nucleic acid molecule of interest. Therefore Dalemans in view of Volkin et al., which are relevant for all its teaching provide reasoning and motivation to include a mineral-based negatively charged adjuvant which will increase the immune response and decrease nuclease digestion of the DNA within the vertebrate host subsequent to immunization.

Applicants argue that the mixing step is not taught, However the immunogenic composition of Dalemans et al, meets the claim limitations. Dalemans et al., teach the DNA + protein complex can be administered by combining the two or admixing to permit one administration wherein the DNA and protein are admixed, just prior to use or when during manufacturing (page 9, lines 8-11).

Applicants assert that one of skill would come up with different alternative instead of the instant claims. However it is the position of the office that one would have a reasonable expectation of success in combining the protein antigen + adjuvant and the polynucleotide immunogenic component since Dalemans and Volkin et al., teach vaccines/immunogenic compositions are well known to comprise negatively charged

mineral-based adjuvants such as aluminum phosphate based adjuvants which carry a sufficiently negative charge in order to substantially retard binding to the polynucleotide component. Moreover, Dalemans et al., in view of Volkin et al., teach an immunogenic composition suitable for administration to a vertebrate host comprising: (a) a composition comprising a protein antigen immunogenic component comprising at least one protein antigen selected from the group consisting of model protein antigens and immunogenic protein antigens and a mineral-based, negatively charged adjuvant; and (b) a polynucleotide immunogenic component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said polynucleotide immunogenic component into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune, said composition produced by a method comprising preincubating or subsequently mixing the mineral-based negatively charged adjuvant with at least one protein antigen immunogenic component to form the composition of (a) prior to formulating with said polynucleotide immunogenic component.

In conclusion, Applicant is reminded that there is no limitation in any claim drawn to differentiating and pre-determining the immunological response. The prior art teach immunogenic compositions that induce a prophylactic or therapeutic immune response having all of the recited components.

Applicants urge that Dalemans only includes a positively charged mineral-based adjuvant in a slow release formulation of the protein vaccine component.

However, Applicant is reminded that Dalemans et al., is not limited to only the teaching of specific exemplars. Rather Dalemans et al., is relevant for all that it discloses. This argument is not persuasive especially when considering that Dalemans et al., disclose recite administration of both DNA and the protein antigen further including alum, as a mineral-based negatively charged adjuvant. Furthermore, Volkin et al., teach the many advantages for the well known and commercially available mineral-based negatively charged adjuvants including: stimulating IL-4 and T_H2-type of helper T cells, increasing levels of IgG1 and IgE antibodies, substantially retard binding to the nucleic acid molecule of interest, and decreasing nuclease digestion of the DNA within the vertebrate host.

Thus, none of applicants arguments are persuasive and the rejection is maintained.

Conclusion

4. No claims allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor Patricia Duffy, can be reached on 571-272-0855. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645